

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problems Mailbox.**



AU9217854

(12) PATENT ABRIDGMENT (11) Document No. AU-B-17854/92  
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 649543


- (54) Title  
COMPOSITION AND METHOD OF TREATING DEPIGMENTATION DISORDERS
- (51)<sup>5</sup> International Patent Classification(s)  
A61K 033/32 A61K 033/14 A61K 033/24 A61K 033/26  
A61K 033/34
- (21) Application No. : 17854/92 (22) Application Date : 15.05.92
- (87) PCT Publication Number : WO92/20354
- (30) Priority Data
- (31) Number (32) Date (33) Country  
9110652 15.05.91 GB UNITED KINGDOM
- (43) Publication Date : 30.12.92
- (44) Publication Date of Accepted Application : 26.05.94
- (71) Applicant(s)  
STIEFEL LABORATORIES, INC.
- (72) Inventor(s)  
JOHN MARTIN WOOD; KARIN UTA SCHALLREUTER
- (74) Attorney or Agent  
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000
- (57) Claim

1. A method of pigmenting skin depigmented by a tyrosinase-positive depigmentation disorder which comprises applying to at least the depigmented areas of the skin an effective amount of a pseudocatalase and thereafter exposing the treated skin to UVB light to induce melanin formation in the depigmented areas.

7. A topical composition comprising a pseudocatalase selected from Cu(I), Fe(II) or Mn(II)-bicarbonate coordination complexes and a physiologically acceptable topical vehicle therefor.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> A61K 33/24, 33/32, 33/34 A61K 33/26	<b>A1</b>	<b>(11) International Publication Number:</b> WO 92/20354 <b>(43) International Publication Date:</b> 26 November 1992 (26.11.92)
<b>(21) International Application Number:</b> PCT/GB92/00878 <b>(22) International Filing Date:</b> 15 May 1992 (15.05.92) <b>(30) Priority data:</b> 9110652.6 15 May 1991 (15.05.91) GB <b>(71) Applicant (for all designated States except US):</b> STIEFEL LABORATORIES, INC. [US/US]; 2801 Ponce de Leon Boulevard, Suite 850, Coral Gables, FL 33134-6988 (US); <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> WOOD, John, Martin [GB/DE]; SCHALLREUTER, Karin, Uta [DE/DE]; Feldbehnkehre 16, D-2085 Quickborn (DE). <b>(74) Agent:</b> BURFORD, Anthony, Frederick; W.H. Beck, Greener & Co., 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB).		<b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), NO, PL, RO, RU, SE (European patent), US.  <b>Published</b> With international search report. The Alhambra International Center 255 Alhambra Circle Suite 1000 Coral Gables, FL 33134 United States of America   <b>649543</b>

**(54) Title:** COMPOSITION AND METHOD OF TREATING DEPIGMENTATION DISORDERS



**BEFORE TREATMENT**



**AFTER TREATMENT**

**(57) Abstract**

Vitiligo and other tyrosinase-positive depigmentation disorders are treated by topical application of a pseudocatalase and subsequent exposure to a sub-minimal erythema dose of UVB light. After a course of treatment, pigmentation of the affected areas can be maintained by treatment with the pseudocatalase without UVB light treatment. The preferred pseudocatalases are transition metal co-ordination complexes, especially manganese (II) bicarbonate

COMPOSITION AND METHOD OF  
TREATING DEPIGMENTATION DISORDERS

5       The present invention relates to the treatment of  
tyrosinase-positive depigmentation disorders and has  
particular application to the treatment of vitiligo. It  
provides compositions for said treatment and methods of  
said treatment.

10

Vitiligo is a chronic depigmentation disorder in which  
the patient has unsightly white patches or spots which are  
caused by localized loss of pigment and are very liable to  
sunburn. Although the condition is not debilitating, it is  
15 often emotionally stressful to the patient. The cause  
presently is unknown but it has been speculated that it  
results from an autoimmune response, involvement of the  
nervous system or a toxic effect on melanocytes. Usually,  
the only treatment is the use of skin-colouring cosmetics  
20 to disguise the patches or, in the case of Blacks and  
Indians, of depigmenting agents such as hydroquinone to  
depigment the remaining pigmented skin. Some limited  
success in treatment has been reported using the so-called  
PUVA method.

25

In the PUVA method, methoxsalen (ie. 8-methoxy  
psoralen) or, less usually, other psoralens is administered  
orally and the patient subsequently exposed to UVA light.  
Psoralens are plant extracts and have been known since  
30 ancient Egyptian times to act as photosensitizers. The  
psoralen is given systemically and hence the  
photosensitizing effect is not localized and, since this  
effect is in the UVA range (320-400 nm), the patient must  
wear special glasses during everyday life in order to  
35 prevent eye damage. Further, side effects of PUVA include  
nausea, erythema, oedema, dizziness, headache,

vesiculation, bulla formation, onycholysis, acneiform eruption and severe skin pain. Long term risks include skin cancer, epidermal dystrophy, premature skin aging, cataract formation, and alterations in the immune system. The treatment is believed to be toxic to normal lymphocytes and Langerhans' cells. Accordingly, the treatment usually is limited to elderly patients or to two years duration. It has recently been proposed to mitigate some of the risks of PUVA by bathing the patient in a psoralen bath.

Other tyrosinase-positive depigmentation disorders include Hermansky-Pudlak Syndrome.

It has now surprisingly been found that vitiligo and other tyrosinase-positive depigmentation disorders can be effectively treated by exposing a patient to UVB light (290-320 nm) after topical application of manganese (II) bicarbonate or other pseudocatalase. Further, it has been found that, following pigmentation by said treatment, a level of pigmentation in affected areas can be retained, at least for a period of time, by topical application of the pseudocatalase without UVB exposure.

We have disclosed in a co-pending Patent Application of the same priority and filing dates and corresponding to UK Patent Application No. 9110651 that pseudocatalase can be used topically to enhance sun tanning.

By pseudocatalase, we mean a plasma membrane permeable physiologically acceptable compound which catalyzes the dismutation of  $H_2O_2$  in vivo in analogous manner to catalase.

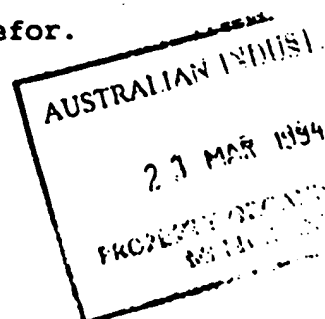
Without wishing to be bound to any particular hypothesis, it is believed that vitiligo and other tyrosinase-positive depigmentation disorders are caused by a deficiency of catalase which permits a higher than normal

peroxide ion concentration in melanocytes. Since tyrosinase is inactivated by peroxide ion, the tyrosinase-catalyzed oxidation of l-tyrosine to l-dopa required for melanin biosynthesis is inhibited. Further, since peroxide ion is photochemically reduced to hydroxyl ion, there is a concomitant increase in hydroxyl ion production.

Exposure of the skin to UVB radiation generates superoxide anion radicals which is a preferred substrate for human tyrosinase (40 times better than oxygen) thereby promoting melanin formation. However, the superoxide anion radicals are dismutated into dioxygen and peroxide ion causing an undesirable increase in hydroxyl ion concentration unless catalase or some other competing mechanism removes peroxide ion. Thus, the presence of a pseudocatalase is believed to allow sufficient UVB exposure for superoxide anion radical formation to promote pigmentation in catalase deficient areas without burning or other cell damage.

According to a first aspect of the present invention, there is provided a method for treating a tyrosinase-positive depigmentation disorder which comprises applying to at least the depigmented areas of the skin of a patient suffering therefrom an effective amount of a pseudocatalase and thereafter exposing the treated skin to UVB light to induce melanin formation in the depigmented areas.

In a second aspect, the invention provides a topical composition comprising a pseudocatalase and a physiologically acceptable topical vehicle therefor.



~~of the skin of a patient suffering therefrom an effective~~  
amount of a pseudocatalase and thereafter exposing the  
treated skin to UVB light to induce melanin formation in  
~~the depigmented areas.~~

5

As mentioned previously, the invention has particular  
application to the treatment of vitiligo but can be applied  
to the treatment of other tyrosinase-positive  
depigmentation disorders, for example Hermansky-Pudlak  
10 Syndrome.

The pseudocatalase can be any physiologically  
acceptable compound which catalyzes the dismutation of  
hydrogen peroxide. Some compounds such as Mn(II)  
15 bicarbonate are already known to be pseudocatalases and  
others can be determined by simple screening tests.

The presently preferred pseudocatalases are transition  
metal co-ordination complexes in which the inductive effect  
20 of the electron acceptor ligand enhances the redox effect  
of the metal on hydrogen peroxide dismutation. Usually,  
the metal will be Cu(I), Fe(II) or, especially Mn(II) and  
the ligand will be bicarbonate. It is especially preferred  
that the pseudocatalase is Mn(II) bicarbonate complex.  
25 Said complex readily can be prepared by contacting  
manganous chloride with excess bicarbonate in aqueous  
solution.

The pseudocatalase is formulated in a topical vehicle  
30 for use. Conveniently, the vehicle comprises a hydrophilic  
cream to which an aqueous solution or suspension of the  
pseudocatalase is added to form a cream or lotion.  
Alternatively, the vehicle can be a bath oil although any  
other compatible topical vehicle can be used to provide a  
35 topical composition.

Preferably, the composition contains calcium ions, suitably added as calcium chloride, to compensate for a calcium defect which appears to be present in vitiliginous skin. Usually, the calcium ion concentration will be 5 to 20 ~~mmol~~ m.m.molar

The composition can contain components such as emollients, perfumes etc conventionally used in topical preparations.

10

Usually, the topical composition is applied twice a day to at least the depigmented areas of skin, usually to the entire skin surface. After at least one of said applications, the patient is exposed to UVB light after a short delay, usually about 20 to 60 minutes, to allow for transport of the pseudocatalase into the epidermis. The UVB exposure is limited to prevent erythema and is increased over the period of treatment from a few seconds to about 5 minutes as the minimal erythema dose increases with UVB tolerance. The course of treatment is continued for several months until there is an acceptable level of pigmentation in the previously depigmented areas. Thereafter, pigmentation is maintained by continuing daily application of the topical composition, possibly with reduced frequency, without UVB exposure. If and when pigment is lost from the affected areas, the exposure to UVB light is recommenced for as long as necessary to restore pigmentation.

30

The invention is illustrated in the following non-limiting Examples.

#### Example I

35

Manganous chloride (380 mg) was added to a solution of sodium bicarbonate (2.3 g) in purified water (3.0 ml) at



ambient temperature. The mixture was allowed to stand until the evolution of gas had ceased. The resultant pinkish brown liquid was mixed with a hydrophilic cream (100 g, Neribase) to provide a white cream.

5

Neribase is a cream vehicle containing Macrogol stearate 2000; stearic alcohol; liquid paraffin; white soft paraffin; polyacrylic acid; sodium hydroxide; disodium EDTA (i.e. ethylenediaminetetraacetic acid disodium salt); methyl and propyl Paraben (i.e. 4-hydroxybenzoic acid methyl and propyl esters); and water.

10

#### Example II

The white cream of Example I was applied twice daily (morning and either afternoon or evening) to the depigmented areas (vitiligo spots) of several patients suffering from vitiligo. After about 20 minutes following one of said applications, the affected areas were exposed to UVB light for a short period of time to provide a sub-minimal erythema dose. As the patient's tolerance to UVB light increased, the exposure time was increased from a few seconds to a maximum of about 5 minutes. In all cases, the vitiligo spots were significantly pigmented after a course of treatment of between 3 and 6 months.

15

20

25

The accompanying Figures I and II show a typical improvement in the vitiligo patients treated. Both figures show the ear of the same patient. When the patient presented at the clinic, she had several large vitiligo spots including one in the region of the right ear (Fig. I). After three months pseudocatalase/ UVB treatment as described above, many of the vitiligo spots had decreased substantially in size including the right ear spot (Fig. II). Pseudocatalase/UVB treatment of this patient continued for a further three months, by which time there

30

35

was a further substantial reduction in size of the vitiligo spots. The patient was then maintained with pseudocatalase treatment alone.

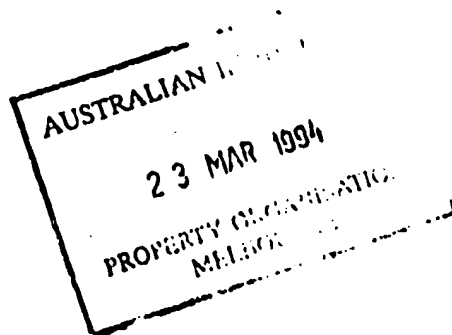
5        Example III

10        The procedure of Example 1 was repeated using creams to which calcium chloride had been added to provide 5 millimolar calcium ion content. 18 patients were treated for a mean duration of 4.2 months; 14 of these patients had a partial response and 2 showed a marked, although not complete, pigmentation of vitiliginous skin areas.

15        Example IV

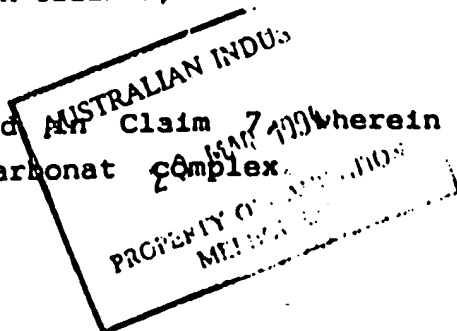
20        The procedure of Example 1 was repeated using creams to which calcium chloride had been added to provide 10 millimolar calcium ion content. 12 patients were treated for a mean duration of 2.25 months; all had a partial response but none showed significant pigmentation of vitiliginous skin areas.

25        Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method of pigmenting skin depigmented by a tyrosinase-positive depigmentation disorder which comprises applying to  
5 at least the depigmented areas of the skin an effective amount of a pseudocatalase and thereafter exposing the treated skin to UVB light to induce melanin formation in the depigmented areas.
- 10 2. A method as claimed in Claim 1, wherein the pseudocatalase is a transition metal co-ordination complex.
3. A method as claimed in Claim 2, wherein the pseudocatalase is a Cu(I), Fe(II) or Mn(II) co-ordination  
15 complex.
4. A method as claimed in Claim 3, wherein the ligand of said co-ordination complex is bicarbonate.
- 20 5. A method as claimed in Claim 4, wherein the pseudocatalase is a Mn(II)-bicarbonate complex.
6. A method as claimed in Claim 5, wherein the Mn(II)-bicarbonate complex has been obtained by contacting manganous  
25 chloride with excess sodium bicarbonate in aqueous solution.
7. A topical composition comprising a pseudocatalase selected from Cu(I), Fe(II) or Mn(II)-bicarbonate co-ordination complexes and a physiologically acceptable topical  
30 vehicle therefor.
8. A composition as claimed in Claim 7, which contains 5 to 20 millimolar calcium ions.
- 35 9. A composition as claimed in Claim 7 wherein the pseudocatalase is a Mn(II)-bicarbonate complex.

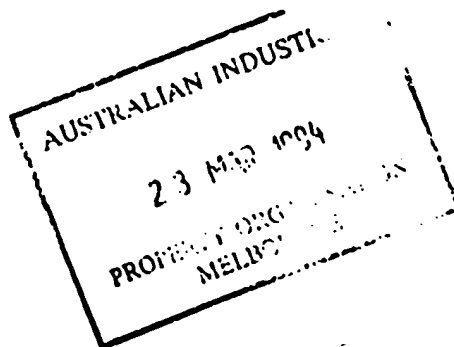


10. A composition as claimed in Claim 9, wherein the Mn(II)-bicarbonate complex has been obtained by contacting manganous chloride with excess sodium bicarbonate in aqueous solution.

5 11. Topical compositions or methods involving them, substantially as hereinbefore described with reference to the Examples and/or drawings.

10 DATED this 23rd day of March, 1994.

STIEFEL LABORATORIES, INC.  
By its Patent Attorneys  
DAVIES COLLISON CAVE



1 / 2



BEFORE TREATMENT

FIG. I

2 / 2

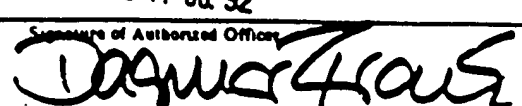


AFTER TREATMENT

FIG. II

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 92/00878

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl.5 A 61 K 33/26	A 61 K 33/24	A 61 K 33/32 A 61 K 33/34
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	EP,A,0424033 (POLA CHEMICAL INDUSTRIES INC.) 24 April 1991, see the whole document ---	1,3-4
A	FR,A,2287899 (L'OREAL) 14 May 1976, see page 3, lines 3-11; page 9, lines 20-21; page 10, lines 1-13; claims ---	1,3-4,9 -11
X	Patent Abstracts of Japan, vol. 14, no. 314 (C-737)[4257], 5 July 1990, & JP,A,2108612 (ZHIZEN K.K.) 20 April 1990, see the abstract ---	1,3-4
A	Patent Abstracts of Japan, vol. 13, no. 308 (C-617)[3656], 14 July 1989, & JP,A,196107 (KANEBO LTD) 14 April 1989, see the abstract ---	1,3-4
X	AU,B, 73343 (WALLICZEK) 25 February 1982, see the whole document --- -/-	1,3-4
<p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, e.g. exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10-07-1992	07.08.92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

(CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,A	STN File Supplier, Karlsruhe DE, File Chemical Abstracts, & CA, vol. 114, no. 21, 27 May 1991, (Columbus, Ohio, US), Y. KONO: "Manganese calatase", see abstract no. 202133d, & KASSEI SANSO, FURI RAJIKARU, 1990, 2(1), 18-26, see the abstract ---	1
A	AU,B, 44552 (HAUSLER) 28 August 1980, see the whole document -----	1



**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9200878  
SA 59486

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/07/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0424033	20-04-91	JP-A- 3204805	06-09-91
FR-A- 2287899	14-05-76	LU-A- 71110	11-11-76
		BE-A- 834483	14-04-76
		CA-A- 1063028	25-09-79
		CH-A- 609862	30-03-79
		DE-A, C 2545986	29-04-76
		GB-A- 1497950	12-01-78
		JP-C- 1336180	11-09-86
		JP-A- 51063949	02-06-76
		JP-B- 59010324	08-03-84
		US-A- 4129644	12-12-78
AU-B- 73343		None	
AU-B- 44552		None	